Drug **Administration, Absorption** & Distribution

2003-2004

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Learning Objectives:

Drug **Administration**:

1. List several enteral and parenteral routes of **administration** and how they influence **absorption** into the circulation.

2. Describe the chemical properites that influence drug **absorption** (via passive diffusion across cell membranes). Explain the effects of molecular weight, lipid solubility, polarity and ionization on passive diffusion. Describe how the degree of ionization changes with pH for an acid and a base. Use the Henderson-Hasselbalch to determine the ratio of protonated to unprotonated forms of an acidic or basic drug at a given pH. Explain how physiologic variables (e.g., pH, blood flow, surface area, gastric motility) influence **absorption**.

3. Describe the properties of other mechanisms of membrane transfer: facilitated diffusion, active transport, endocytosis.

4. Understand the concept of "bioavailability" of an oral dose and how this is determined.

Drug Distribution:

1. Explain how adipose tissue, plasma proteins, bone and transcellular sites (e.g., stomach) may serve as drug reservoirs. For each reservoir, describe the mechanism in as much detail as you can, and give an example of a pertinent drug. Describe the importance of placental transfer.

2. What are the volumes of body water compartments in an average person? Define volume of distribution and show how it is calculated. Why is this called "apparent" volume of distribution? What drug properties and physiological conditions influence volume of distribution?

3. Define clearance, discuss its importance, and show how it can be determined.

Pharmacokinetics: The summation of drug **absorption**, distribution, metabolism and elimination. These processes involve passage of drug across the barriers presented by cell membranes.

Drug Characteristics important to consider with regard to ability to cross biological membranes include: degree of ionization, relative lipid solubility of its ionized & nonionized forms, size and shape. The

plasma membrane is a lipid bilayer with the hydrophobic fatty acid chains oriented within the bilayer, providing the continuous hydrophobic phase of the membrane. The hydrophilic head groups of the lipids are oriented "outward" (towards both the cytoplasm and the extracellular space). Proteins are embedded in the bilayer; some proteins are receptors.

Physiologic Characteristics that influence **absorption** include pH, area of absorbing surface, gastric motility, and ingestion with or without food (for oral **administration**), presystemic elimination, and blood flow at site of **absorption**.

ABSORPTION AND ROUTES OF DRUG ADMINISTRATION

Enteral administration

Oral ingestion: 100% of the dose is subject to first-pass elimination. **Absorption** occurs via passive diffusion and is governed by blood flow, surface area, drug concentration & formulation. All things being equal (which they are NOT), drugs that are weak acids would be optimally absorbed from the acid environment of the stomach, and drugs that are weak bases from the alkaline environment of the intestine. The stomach serves mainly a digestive function, however. Its small surface area and thick mucosa limit **absorption**. In contrast, as a result of the huge surface area of the intestines, the rate of **absorption** of ALL drugs is greater in the intestines. Changes in the rate of gastric emptying influence rate of presentation of drug to the intestine, and therefore influence rate of **absorption**. In summary, even though the nonionized form of a drug is absorbed more rapidly than the ionized form at any particular site in the GI tract, the *OVERALL RATE* of **absorption** of a drug from the intestine > that from the stomach even if the drug is relatively more ionized in the intestine than in the stomach.

Sublingual: important for certain uncharged, lipid-soluble drugs such as nitroglycerin. Due to venous drainage to superior vena cava, this route protects from first-pass hepatic metabolism.

Rectal: Useful in a vomiting or unconscious patient. About 50% of the absorbed dose will bypass the liver. Drawbacks are irregular and incomplete **absorption** with irritation of mucosa.

Parenteral administration: Intravenous, intraarterial, **subcutaneous**, intramuscular, intraperitoneal, and intrathecal injections.

Subcutaneous: Slow and constant **absorption**. Slow-release pellet may be implanted. Drug must be non-irritating.

Intramuscular: Generally rapid rate of **absorption** from aqueous solution depending on the muscle. Injection of drug solution in oil results in very slow, constant **absorption**.

Intraarterial: Localizes drug effect to an organ/tissue. Requires great care and is of dubious therapeutic value.

Intrathecal: Bypasses blood-brain-barrier. Allows for local and rapid effects of drugs on meninges and CNS.

Intraperitoneal: Peritoneal cavity provides a large absorptive surface. Limited clinical value. Danger of infection is too great. Common route in rodent laboratory studies.

Pulmonary **absorption**: For gaseous/volatile drugs; instantaneous **absorption**; local application; avoids first-pass liver metabolism.

Topical application: Applied to mucous membranes or skin for local effects, although systemic **absorption** may be the goal in some cases.

Physicochemical Factors in Drug Transfer Across Membranes.
Because most drugs pass through cells and not between them, it is important to consider how this transmembrane passage is accomplished, and the general properties of drug molecules and cell membranes that influence this movement.

Drugs cross membranes either by passive or active (energy-dependent) processes.

Passive diffusion: the drug diffuses down its concentration gradient in a manner proportional to its solubility in the membrane (estimated by its oil:water partition coefficient) and its concentration gradient across the membrane. Most drugs are weak electrolytes (ionizable at biological pH's). *The unionized form is usually lipid-soluble and can diffuse across membranes. The ionized form is generally not lipid-soluble and thus unable to diffuse across the membrane.* Therefore, the degree of diffusion also depends on the pK_a of the drug molecule and the pH difference across the membrane.

Molecular Size: Diffusion coefficient is inversely related to the square root of the molecular weight. Thus, for passive diffusion, small drug molecules tend to diffuse across membranes more readily than large molecules (for a given lipid-solubility; see below).

Lipid Solubility: The oil:water partition coefficient is an estimate of this property. The higher the lipid solubility, the greater its transmembrane diffusion.

Degree of Ionization: For weak electrolytes (most drugs), the fraction nonionized depends on its pKa and the pH of the local environment. Remember this: acids (R-COOH) are increasingly ionized ($R\text{-}COO^-$) as pH increases. Bases ($R\text{-}NH_2$) are increasingly ionized ($R\text{-}NH_3^+$) as pH decreases.

- Henderson-Hasselbalch Equation: $pK_a - pH = \log$ (protonated form/nonprotonated form). The relevance of this relationship for acidic and basic drugs will be discussed in class.

Facilitated diffusion: A carrier-mediated process that does NOT require energy, and cannot occur against the concentration gradient of the carried substance. A carrier is a membrane protein.

Active transport: A carrier-mediated process that DOES require energy, involves movement AGAINST the concentration gradient, is selective, may be competitively blocked by congeners, and is saturable. Prevalent in neuronal membranes, choroid plexus, hepatocytes, renal tubule.

Endocytosis, Exocytosis, Internalization: In endocytosis, the plasma membrane pinches off to form a vesicle, which is thereby internalized. In exocytosis, a cytoplasmic vesicle fuses with the plasma to release its contents.

Drug Absorption: Rate and extent to which a drug *leaves* its site of **administration**.

Biovailability: Extent to which a drug *reaches* its site if action (estimated by its appearence in

plasma). Determined from 100 X [AUC (oral)/AUC (i.v.)], where AUC = area under the $[drug]_{plasma}$ vs. time disappearance curve.

Bioequivalence: Pharmaceutically equivalent drug products are considered *bio*equivalent when the rates and extents of bioavailability of the active ingredient do not differ.

DRUG DISTRIBUTION

Once a drug is absorbed into the bloodstream, it may be distributed to interstitial and cellular fluids. The pattern of drug distribution reflects various physiological factors as well as the physicochemical properties of the drug.

The first phase of distribution reflects cardiac output and regional blood flow. Thus, heart, liver, kidney and brain receive most of the drug during the first few minutes after **absorption**. Delivery to muscle, most viscera, skin and adipose is slower, and involves a far larger fraction of the body mass.

Drug reservoirs: Body compartments that a drug accumulates in serve as drug reservoirs and may have effects on drug availability.

Binding to plasma proteins. Albumin binds certain acidic drugs; α_1-acid glycoprotein binds certain basic drugs. Binding of drugs to other plasma proteins is much less extensive. Plasma protein binding influences a drug's inter-compartmental distribution because *only unbound drug may passively diffuse* from plasma into tissue. Active transport, however, is not influenced by plasma protein binding. Plasma protein binding is almost always reversible so that there is an equilibrium established between bound and free drug.

Cellular reservoirs: Drugs may accumulate in muscle, adipose, bone, stomach, intestines; these tissues may represent sizable drug reservoirs if drug binding to tissue is reversible.

Fat: an important reservoir for lipid-soluble drugs (e.g., thiopental).

Bone: Can be a reservoir for slow release into the blood of toxic agents such as lead. Tetracycline and heavy metals accumulate due to initial adsorption onto bone, and subsequent incorporation into the crystal lattice.

Transcellular reservoirs: Drugs may cross epithelial cells and accumulate in transcellular fluids, especially those of the GI tract.

Redistribution: Movement between compartments after initial distribution.

Placental transfer: Drugs cross the placenta primarily by simple passive diffusion. Lipid-soluble, nonionized drugs readily enter the fetal blood. Drug transfer tends to increase towards term as tissue layers between maternal blood and fetal capillaries thin. Thus, the placenta is not a barrier to drugs: the fetus is to some extent exposed to all drugs taken by the mother.

CLINICAL PHARMACOKINETICS

Fundamental hypothesis: a relationship exists between the pharmacological or toxic response to a drug and the accessible concentration of the drug (e.g., in blood).

Volume of Distribution (V_d): relates the amount of drug in the body (mg) to the concentration of drug (C, mg/ml) in the circulating plasma. V_d = amount of drug in body (dose) / C_o. This volume is a *calculated space* and does not necessarily reflect an identifiable physiological volume – it refers to the fluid volume that would be required to contain all of the drug in the body if drug concentration throughout the body were the same as that measured in plasma. The significance of this measurement as well as specific body fluid compartments are discussed in lecture, as is the example of the V_d for digoxin.

Clearance (*CL*): is the most important concept to consider when a rational regimen for long-term drug **administration** is designed. The clinician usually wants to maintain the steady-state drug concentration (C_{ss}) within a known therapeutic range.

Dosing rate = $CL \times C_{ss}$ (Note: this was termed "Maintenance Dose" in Quant. Aspects II)

Clearance of a given drug is usually constant over its therapeutic range of concentrations. This is true for drugs whose elimination follows *first-order kinetics* (discussed under Drug Elimination).

CL = (*rate of elimination / concentration in a given biological fluid*)

Clearance is expressed as volume per unit time. It does NOT indicate how much drug is removed. It indicates the volume of biological fluid that is completely freed of drug to account for elimination per unit time. Clearance is further expressed as blood clearance (CL_b), plasma clearance (CL_p), renal clearance (CL_{renal}), etc.

Various organ clearances are additive: $CL_{plasma} = CL_{renal} + CL_{hepatic} + CL_{other\ (saliva,\ sweat)}$

Extraction Ratio: If Q = organ blood flow, C_A = arterial drug concentration, C_V = venous drug concentration, then rate of elimination for that organ = $(Q \times C_A) - (Q \times C_V) = Q(C_A - C_V)$.

Dividing this equation by concentration of drug entering the organ yields an expression for clearance of the drug by that organ: $CL_{organ} = Q(C_A - C_V/C_A) = Q \times E$. E is referred to as the *extraction ratio*, and is usually used in the context of removal of drug by the liver. We will refer to this again under Drug Elimination.

Related Reading

Goodman & Gilman 10th Edition:
(Physicochemical factors and membrane transport), pp. 3-5
(Drug **Absorption**, bioavailability and **administration**), pp. 5-8
(Distribution Clearance), pp. 8-11 and 18-22

Brody et al., pp. 61-64